

Form PTO-1390  
(Rev. 5-93)

US DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NO.

H.4148 PCT/US

TRANSMITTAL LETTER TO THE UNITED STATES  
DESIGNATED/ELECTED OFFICE (DO/EO/US)  
CONCERNING A FILING UNDER 35 U.S.C. 371

U.S. APPLICATION NO. (if known) 35 U.S.C. 1.5

09/856835

INTERNATIONAL APPLICATION NO.  
PCT/EP00/03758INTERNATIONAL FILING DATE  
April 26, 2000PRIORITY DATE CLAIMED  
May 5, 1999  
May 28, 1999

## TITLE OF INVENTION

NOVEL SALICYL ALCOHOL DERIVATIVES

## APPLICANT(S) FOR DO/EO/US

Ralf OTTO and Albrecht WEISS

Applicant herewith submits to the United States Designated/Elected Office (EO/DO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39 (1).
  - ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
  - ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2)).
    - a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
    - b. ☒ has been transmitted by the International Bureau.
    - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
  - ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
  - ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
    - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
    - b. ☐ have been transmitted by the International Bureau.
    - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
    - d. ☒ have not been made and will not be made.
  - ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
  - ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)). UNEXECUTED
  - ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

## Items 11. to 16. below concern other document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A **FIRST** preliminary amendment
  - ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items or information.:

Drawings - 2 pages

"Express Mail" mailing label number EL 843287387 US

U.S. Application No. (If known see CFR1.30) <div style="font-size: 1.5em; font-weight: bold; margin-left: 100px;">09/856835</div>	INTERNATIONAL APPLICATION NO. <b>PCT/EP00/03758</b>	ATTORNEY'S DOCKET NUMBER <b>H 4148 PCT/US</b>
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17. ■ The following fees are submitted:

**Basic National Fee (37 CFR 1.492(a)(1)-(5)):**

Search Report has been prepared by the EPO or JPO.....\$860.00

International preliminary examination fee paid to USPTO (37CFR 1.482) .....\$670.00

No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37CFR 1.445(a)(2)).....\$690.00

Neither international preliminary examination fee (37CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO....\$970.00

International preliminary examination fee paid to USPTO (37CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4).....\$96.00

**ENTER APPROPRIATE BASIC FEE AMOUNT =**

Surcharge of **\$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date 37 (CFR 1.492(e)).

Claims	Number filed	Number Extra	Rate		
Total Claims	12 - 20 =	0	0 X \$18.00	\$ 0	00
Independent Claims	1 - 3 =	0	0 X \$80.00	\$ 0	00
Multiple dependent claims (s)(if applicable) 0			+ \$260.00	\$ 0	00
<b>TOTAL OF ABOVE CALCULATIONS =</b>				\$ 860	00
Reduction by ½ for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				\$ 0	00
<b>SUBTOTAL =</b>				\$ 860	00
Processing fee of <b>\$130.00</b> for furnishing the English translation later the <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37CFR 1.492(f)).				\$ 0	00
<b>TOTAL NATIONAL FEE =</b>				\$ 860	00
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property				\$ 0	00
<b>TOTAL FEES ENCLOSED =</b>				\$ 860	00
				Amount to be: refunded	\$ _____
				charged	\$860.00

a. ☐ A check in the amount of \$ \_\_\_\_\_ to cover the above fees is enclosed.

b. ■ Please charge my Deposit Account No. 01-1250 in the amount of \$860.00 to cover the above fees. A triplicate copy of this sheet is enclosed. Order No. 01-0417.

c. ■ The Assistant Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 01-1250. A triplicate copy of this sheet is enclosed.

**NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.**

SEND ALL CORRESPONDENCE TO: Henkel Corporation, Law Dept.  
2500 Renaissance Blvd, Suite 200  
Gulph Mills, PA 19406

SIGNATURE

Glenn E. J. Murphy  
 NAME ATTORNEY FOR APPLICANT  
 33,539  
 REGISTRATION NUMBER

Express Mail  
Label No. EL 843287387 US

PATENT  
Docket H 4148 PCT/US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Re: PCT/EP00/03758

International Filing Date: April 26, 2000  
Priority Date: May 5, 1999 and May 28, 1999  
Applicant: OTTO, et al.  
Title: NOVEL SALICYL ALCOHOL DERIVATIVES

PRELIMINARY AMENDMENT

Assistant Commissioner of Patents  
Washington, DC 20231

Please enter the amendments below before examining this  
case on the merits:

IN THE SPECIFICATION:

On page 1, insert below the title:

--CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a U.S. National Stage application  
filed under 35 U.S.C. § 371, claiming priority under 35  
U.S.C. §§ 119 and 365 of International Application No.  
PCT/EP00/03758, filed April 26, 2000, in the European Patent  
Office and DE 199 20 558.2 and DE 199 24 688.2, filed  
respectively on May 5 and May 28, 1999, in the German Patent  
Office.--

On page 3, between lines 2 and 3, insert:

--BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 plots the influence of phenylpropionyl salicin  
(lower solid-line curve) and p-OH-phenylacetyl salicin

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(upper dotted-line curve) on the vitality of skin cells  
(keratinocytes).

Figure 2 shows the inhibiting effects of salicin and  
salicin esters on the release of prostaglandins in  
keratinocytes.

DESCRIPTION OF THE INVENTION--.

IN THE ABSTRACT:

Please add to the application as a separate page  
following the claims the abstract appended to this paper.

IN THE CLAIMS:

Please cancel claims 1-11 without prejudice, and add  
new claims 12-23:

12. A salicyl alcohol derivative of the formula (I):



in which  $R^1$  is a hydrogen atom or a  $C(O)R^3$  group where  $R^3$  is  
an alkyl, cycloalkyl, cycloalkylalkyl, aralkyl or aryl group  
containing 1 to 26 carbon atoms and/or 1-10 hetero atoms  
which may be unbranched or branched, mono- or  
polyunsaturated and/or may bear substituents on the carbon  
chain and/or at the hetero atoms,

Ph is a 1,2-phenylene group,

Z is a sugar hemiacetally attached to the aromatic group Ph  
in (I) and optionally substituted n-times by  $R^2$  like an

ester; the sugar may be a mono-, di-, oligo- or polysaccharide,

n is an integer between 0 and m, m being equal to the number of free hydroxyl groups present in the sugar Z hemiacetally attached to the aromatic group,

$R^2$  is a hydrogen atom or a group  $C(O)R^4$  where  $R^4$  is selected from the same group as  $R^3$ ;  $R^1$  and  $R^2$  may be the same or different, with the proviso that at most one of the two substituents  $R^1$  or  $R^2$  is hydrogen when Z is glucose,

and on the conditions that

where Z is glucose and  $R^2$  is hydrogen,  $R^1$  cannot be acetyl or benzoyl or (1-hydroxy-6-oxo-2-cyclohexen-1-yl)carbonyl and, where  $R^1$  is hydrogen, Z is glucose and  $n = 1$  and the glucose unit is substituted by  $R^2$  at its primary hydroxy group,  $R^2$  cannot be 4-phenylbutyryl.

13. The salicyl alcohol derivative of claim 12, wherein at least one of the two substituents  $R^1$  and  $R^2$  is a hydrogen atom, or a benzoyl, phenylacetyl, phenylpropionyl, phenylbutyryl, phenylvaleroyl, o-, m- or p-hydroxybenzoyl, o-, m- or p-hydroxyphenylacetyl, o-, m- or p-hydroxyphenylpropionyl, o-, m- or p-hydroxyphenylbutyryl, o-, m- or p-hydroxyphenylvaleroyl, 3,4,5-trihydroxybenzoyl, 3-phenylacryloyl, o-, m- or p-hydroxy-3-phenylacryloyl or 3-(3,4-dihydroxyphenyl)-acryloyl group.

14. The salicyl alcohol derivative of claim 12, wherein  $n = 1$  and  $R^1$  is hydrogen.

15. The salicyl alcohol derivative of claim 13, wherein  $n = 1$  and  $R^1$  is hydrogen.

16. The salicyl alcohol derivative of claim 12, wherein Z

is a monosaccharide selected from the group consisting of threose, erythrose, arabinose, lyxose, ribose, xylose, allose, altrose, galactose, glucose, gulose, idose, mannose, talose, and fructose.

17. The salicyl alcohol derivative of claim 16, wherein Z is D-glucose.

18. The salicyl alcohol derivative of claim 12, wherein R<sup>1</sup> is hydrogen, Z is glucose, and n = 1, the glucose is substituted by R<sup>2</sup> = C(O)R<sup>4</sup> at its primary hydroxy group, and R<sup>4</sup>COOH is not a hydrophobic aromatic carboxylic acid.

19. A process for the production of the salicyl alcohol derivative of claim 12, comprising the steps of esterifying or transesterifying with a carboxylic acid R<sup>3</sup>COOH and/or R<sup>4</sup>COOH, a carboxylic acid ester R<sup>3</sup>COOR<sup>5</sup> and/or R<sup>4</sup>COOR<sup>5</sup>, or an activated carboxylic acid derivative, an alcohol of the formula (II):



where Ph, Z, R<sup>3</sup>, R<sup>4</sup>, and R<sup>5</sup> are as defined for formula (I), in the presence of a suitable catalyst.

20. The process of claim 19, carried out by enzyme-catalyzed esterification or transesterification.

21. A method of preparing a cosmetic or pharmaceutical preparation, comprising the steps preparing the salicyl alcohol derivative of claim 12, and combining said derivative with a cosmetically or pharmaceutically acceptable carrier.

22. A method of inhibiting prostaglandin synthesis, comprising the steps of applying a prostaglandin synthesis inhibitive amount of a cosmetic or pharmaceutical preparation comprising preparing the salicyl alcohol derivative of claim 12 to a host in need of prostaglandin synthesis inhibition.

23. A cosmetic or pharmaceutical preparation, comprising the salicyl alcohol derivative of claim 12 in a cosmetically or pharmaceutically acceptable carrier.

REMARKS

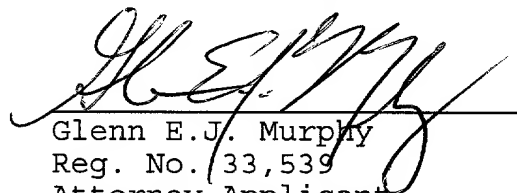
Claims 1 to 11 have been canceled without prejudice, and new claims 12-23 added. The new claims are described in the specification at page 3, line 9 to page 4, line 11, page 5, lines 7 to page 6, line 16, and page 7, line 27 to page 8, line 13, as well as in the original claims. The specification has been amended to include a cross- reference to related applications and other headings appropriate to U.S. practice. No new matter has been added.

The new claims better claim the full literal and equivalent scope and breadth of subject matter disclosed in the application, notwithstanding applicants' belief that the original claims, drafted for examination in the German and European Patent Offices, would have been allowable but for minor matters of form, such as multiple dependency, multiple preferred embodiments in a single claim, and transitional phrases permitted in German practice but objected to in the U.S.P.T.O. The new claims find support in the application independent of the original claims and therefore are not believed to constitute narrowing amendments to the original

claims within the holding of Festo Corp. v. Shoketsu Kinzoku  
Kogyo Kabushiki Co., No. 95-1066 (Fed. Cir. Nov. 29, 2000).

Applicants respectfully request entry of this Amendment  
and examination of the application. If any fees are due to  
enter this paper that have not been accounted for, please  
charge Deposit Account No. 01-1250.

Respectfully submitted,

  
Glenn E.J. Murphy  
Reg. No. 33,539  
Attorney Applicant  
(610) 278-4926

Henkel Corporation  
Patent Department  
2500 Renaissance Blvd., Suite 200  
Gulph Mills, PA 19406



2/PR TS

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JC18 Rec'd PCT/PTC 25 MAY 2001  
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WO 00/68239

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### Novel Salicyl Alcohol Derivatives

This invention relates to new salicyl alcohol derivatives, to processes for their preparation and to cosmetic and/or pharmaceutical preparations containing these compounds.

Many naturally occurring alkyl and phenol glucosides show antiviral, antimicrobial and, in some cases, anti-inflammatory effects (S. Matsamura, K. Imai, K. Kawada and T. Uchibori, Surface activities, biodegradability and antimicrobial properties of n-alkyl-glucosides, mannosides and galactosides, **J. Am. Oil Chem. Soc.** 67, 996-1001 (1990); T. Hedner and B. Everts, The early clinical history of salicylates in rheumatology and pain, **Clin. Rheumatol.** 12, 17-25 (1998)). Above all, aqueous extracts of willow bark (*Salix alba*, *purpurea* or *fragilis*) and poplar are known to have anti-inflammatory activity. Accordingly, corresponding extracts are used in medicinal teas and in cosmetic products, for example to reduce irritation of the skin, as described in German patent application **DE 196 15 577**. Important ingredients of willow bark include salicin and salicylic acid (o-hydroxybenzoic acid), salicortin (2-[[[(1-hydroxy-6-oxo-2-cyclohexen-1-yl)-carbonyl]oxy]methyl]phenyl-β-D-glucopyranoside) and fragilin (acetyl salicin) while the bark of poplars contains populin (benzoyl salicin). In the main, salicylic acid and its derivatives, such as acetyl salicylic acid, have been very thoroughly investigated for anti-inflammatory activity. As non-steroidal anti-inflammatory drugs (NSAID), they inhibit prostaglandin synthesis (J.R. Vane, Inhibition of prostaglandin synthesis as a mechanism of action of the aspirin-like drugs, **Nature**, 231, 232-235 (1971)).

Prostaglandins are formed as a reaction to various exogenous cell-specific stimuli by deoxygenation of polyunsaturated fatty acids, more particularly arachidonic acid, catalyzed by the enzymes prostaglandin-synthase-1 and -2 (PGHS-1 and -2). As autocrinal and paracrine tissue hormones, they are formed to a greater extent in cases of injury or skin irritation, in wound healing processes and in inflammatory reactions.

Normal epidermis already contains significant quantities of prostaglandins which are evidently formed by PGHS-1 because PGHS-2 is not expressed. In irritated skin, prostaglandins (above all PGE<sub>2</sub> and PGF<sub>2</sub> $\alpha$  from the keratinocytes) as local inflammation mediators promote both the dilation (widening) and also greater permeability of blood vessels and are thus involved in the reddening, heating and swelling of the skin typical of inflammation reactions (G. Fürstenberger, Role of eicosanoids in mammalian skin epidermis, **Cell. Biol. Rev.** **24**, 1-90 (1990); G. Fürstenberger, V. Kinzel, M. Schwarz and F. Marks, Partial inversion of the initiation-promotion sequence of multistage tumorigenesis in the skin of NMRI mice; **Science** **230**, 76-78 (1985)) and in the development of a regenerative epidermal hyperplasia. Prostaglandin synthesis inhibitors are capable of preventing these unwanted effects.

Besides the salicin derivatives occurring in willow and poplar mentioned at the beginning, the isolation of benzoyl salicin from plants is known from the literature (L. van Hoof et al., Plant viral agents, VI. Isolation of antiviral phenolic glucosides from *Populus cultivar Beaupre* by droplet counter-current chromatography, **J. Nat. Prod.** **52**, 875-878 (1989)) as is the enzymatic production of phenyl butyryl salicin (R.T. Otto, U.T. Bornscheuer, C. Syldatk and R.D. Schmid, Lipase-catalyzed synthesis of arylaliphatic esters of D(+)-

glucose, alkyl- and aryl-glucosides and characterization of their surfactant properties; **J. Biotechnol.** 64, 231-237 (1998)).

Although numerous pharmacologically active substances intervening, for example, in the inflammation cascade are already known in the literature, there is still a need for more effective active principles with minimal side effects. There is also a need for active principles which are readily absorbed by and rapidly penetrate into the skin and which, in addition, must readily lend themselves to incorporation in pharmaceutical or cosmetic formulations.

It has now surprisingly been found that certain salicyl alcohol derivatives, which may be regarded from their chemical structure as related to salicin, show cosmetically and pharmaceutically useful pharmacological effects such as, for example, anti-inflammatory, antipyretic, antiphlogistic and/or analgesic effects and have fewer, if any, of the above-described disadvantages of the prior art.

The present invention relates to salicyl alcohol derivatives corresponding to general formula (I):



to processes for their production and to cosmetic or pharmaceutical preparations containing these compounds. The compounds show valuable pharmacological properties such as, for example, an inhibiting effect on prostaglandin synthesis. In general formula (I):

$R^1$  is a hydrogen atom or a  $C(O)R^3$  group where  $R^3$  is an alkyl, cycloalkyl, cycloalkylalkyl, aralkyl or aryl group containing 1 to 26 carbon atoms and/or 1-10 hetero atoms which may be unbranched or branched, mono- or

polyunsaturated and/or may bear substituents on the carbon chain and/or at the hetero atoms,

Ph is the 1,2-phenylene group,

Z is a sugar hemiacetally attached to the aromatic group Ph in (I) and

5 optionally substituted n-times by  $R^2$  like an ester; the sugar may be a mono-, di-, oligo- or polysaccharide,

n is an integer between 0 and m, m being equal to the number of free hydroxyl groups present in the sugar Z hemiacetally attached to the aromatic group,

10  $R^2$  is a hydrogen atom or a group  $C(O)R^4$  where  $R^4$  is selected from the same group as  $R^3$ ;  $R^1$  and  $R^2$  may be the same or different with the proviso that at most one of the two substituents  $R^1$  or  $R^2$  is hydrogen when Z is glucose, and on the conditions that

where Z is glucose and  $R^2$  is hydrogen,  $R^1$  cannot be acetyl or benzoyl or (1-hydroxy-6-oxo-2-cyclohexen-1-yl)carbonyl and, where  $R^1$  is hydrogen, Z is  
15 glucose and n = 1 and the glucose unit is substituted by  $R^2$  at its primary hydroxy group,  $R^2$  cannot be 4-phenylbutyryl. Where  $R^1$  is hydrogen, Z is glucose and n = 1 and the glucose unit is substituted by  $R^2$  at its primary hydroxy group, the carboxylic acid  $R^4COOH$  corresponding to the substituent  $R^2$  is preferably not a hydrophobic aromatic carboxylic acid.

20 The meanings mentioned at the beginning in the definition of the substituents include, for example,

for  $R^3$  and  $R^4$ : hydrogen, the methyl, ethyl, propyl, n-butyl, tert.butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, heneicosyl, vinyl, 1-propenyl, 2-  
25 propenyl, 2-butenyl, 8-pentadecenyl, 8-heptadecenyl, Z,Z-8,11-heptadecadienyl, Z,Z,Z-8,11,14-heptadecatrienyl, 4,7,10,13,16-

nonadecapentaenyl, 3,6,9,12,15,18-heneicosahexaenyl, phenyl, phenylmethyl, phenylethyl, phenylpropyl, phenylbutyl, o-, m- or p-hydroxyphenyl, o-, m- or p-hydroxyphenylmethyl, o-, m- or p-hydroxyphenylethyl, o-, m- or p-hydroxyphenylpropyl, o-, m- or p-hydroxyphenylbutyl, 3,4,5-trihydroxyphenyl, 3-phenylvinyl, o-, m- or p-hydroxy-3-phenylvinyl, 3-(3,4-dihydroxyphenyl)-vinyl or 3-pyridyl group, additional substituents such as, for example, a halogen atom, an alkyl, hydroxy, alkoxy, phenyl, nitro, amino, acetylamino or carboxy group optionally being present, and phenolic hydroxy groups optionally being present as phenolate salts with alkali metal or alkaline earth metals.

Accordingly, the present invention also relates to salicyl alcohol derivatives corresponding to general formula (I) in which at least one of the two substituents  $R^1$  and  $R^2$  is a hydrogen atom, the benzoyl, phenylacetyl, phenylpropionyl, phenylbutyryl, phenylvaleroyl, o-, m- or p-hydroxybenzoyl, o-, m- or p-hydroxyphenylacetyl, o-, m- or p-hydroxyphenylpropionyl, o-, m- or p-hydroxyphenylbutyryl, o-, m- or p-hydroxyphenylvaleroyl, 3,4,5-trihydroxybenzoyl, 3-phenylacryloyl, o-, m- or p-hydroxy-3-phenylacryloyl or 3-(3,4-dihydroxyphenyl)-acryloyl group.

Preferred salicyl alcohol derivatives corresponding to general formula (I) are those in which  $n = 1$  and  $R^1$  is hydrogen.

The substituent Z in general formula (I) may be selected, for example, from threose, erythrose, arabinose, lyxose, ribose, xylose, allose, altrose, galactose, glucose, gulose, idose, mannose, talose, fructose, the naturally occurring stereoisomers of the sugars being preferred, and the di-, oligo- and polysaccharides consisting of these sugars.

Preferred salicyl alcohol derivatives corresponding to general formula (I) are those in which Z stands for D-glucose.

In principle, the compounds according to the invention may be prepared, for example, by any of the processes described in the literature for the production of carboxylic acid esters (cf. C. Ferri, **Reaktionen der organischen Synthese**, Thieme-Verlag, Stuttgart 1978) although they are preferably prepared by esterifications, transesterifications and acylations with activated carboxylic acid derivatives.

Accordingly, the present invention also relates to a process for the production of the compounds (I) according to the invention which is characterized in that an alcohol component is esterified or transesterified with a carboxylic acid, a carboxylic acid ester or an activated carboxylic acid derivative in the presence of suitable catalysts.

An activated carboxylic acid derivative in the context of the invention is understood to be, for example, a carboxylic acid chloride or carboxylic anhydride which may be reacted with an alcohol component under Schotten-Baumann conditions to form an ester.

The compounds according to the invention may be prepared, for example, by esterification of an alcohol corresponding to formula (II)



with a carboxylic acid  $\text{R}^3\text{COOH}$  and/or  $\text{R}^4\text{COOH}$  in which Ph, Z,  $\text{R}^3$  and  $\text{R}^4$  are as defined for formula (I); in the case of esterification with both carboxylic acids, the esterification may be carried out in a single step or even in two successive steps.

In addition, the compounds according to the invention may be prepared by transesterification of an alcohol corresponding to formula (II) with carboxylic

acid esters  $R^3COOR^5$  and/or  $R^4COOR^5$  in which Ph, Z,  $R^3$  and  $R^4$  are as defined for formula (I) and  $R^5$  is an alkyl group containing 1 to 4 carbon atoms; in the case of transesterification with both carboxylic acid esters, the transesterification may be carried out in a single step or even in two successive steps.

In the preparation of the compounds according to the invention by the standard methods of chemical synthesis, mixtures of mono- and poly-substituted products are generally formed on account of the presence of several free hydroxyl groups in the alcohol component (II) or a partial ester thereof, so that protective groups have to be introduced and removed if a particular compound is to be specifically synthesized.

The use of activated carboxylic acid derivatives results in the formation of by-products and, in many cases, also unwanted secondary products which complicate working up, reduce the yields of desired product and pollute the environment. These disadvantages can be avoided or at least reduced by carrying out the production of the compounds according to the invention enzymatically (for example by the process described in German patent application **DE 197 53 789.8**) or by biotransformations with plant cell cultures (M. Ushiyama, S. Kumagai and T. Furuya, **Phytochemistry** 28, 3335 (1989)).

Accordingly, the present invention also relates to a process for the production of the compounds (I) according to the invention which is characterized in that an alcohol component is esterified or transesterified with a carboxylic acid or a carboxylic acid ester in the presence of one or more enzymes as catalysts.

Suitable enzymatic esterification or transesterification processes are described, for example, in K. Drauz and H. Waldman, **Enzyme Catalysis in**

**Organic Synthesis, VCH-Verlag, Weinheim 1975.**

The salicyl alcohol derivatives according to the invention have valuable biological activities such as, for example, anti-inflammatory, antipyretic, antiphlogistic or analgesic effects. Thus, prostaglandin synthesis is inhibited to a greater extent with the compounds according to the invention than, for example, with compounds known from the literature, such as salicin, which is associated with the greater lipophilia of the compounds according to the invention. The better effect is dependent inter alia on efficient absorption by the cell membranes of the keratinocytes. The lipid solubility of glycosidic compounds derives from the ratio of hydrophilic component to hydrophobic component which is described by the HLB value. Salicin which has an HLB value of about 12 is more of a water-soluble molecule whereas salicin esters with HLB values of, in some cases, well below 10 are more liposoluble molecules. As a result, transport through the cell membranes is distinctly improved in relation to salicin while cutaneous application is facilitated or actually made possible in relation to conventional active principles which, in general, only develop an adequate effect with subcutaneous application.

The carboxylic acid component of the salicyl alcohol derivatives according to the invention can be formed by a carboxylic acid  $R^3\text{COOH}$  and/or  $R^4\text{COOH}$  which itself has intrinsic biological activity such as, for example, sorbic acid, a known fungistatic agent. Salicyl alcohol derivatives which show other biological effects, for example antioxidative, skin-lightening, antibacterial, antiviral and fungistatic effects, besides anti-inflammatory, antipyretic, antiphlogistic and analgesic effects, can be obtained in this way.

In addition, the compounds according to the invention can be incorporated particularly well in lipophilic basic formulations and may readily



be formulated as stable emulsions.

According to the invention, the compounds of general formula (1) are used for the production of cosmetic and/or pharmaceutical preparations.

Accordingly, the present invention also relates to cosmetic and/or  
5 pharmaceutical preparations containing the salicyl alcohol derivatives (I) according to the invention.

The cosmetic preparations obtainable using the compounds (I) in accordance with the invention, for example hair shampoos, hair lotions, foam  
10 baths, shower baths, creams, gels, lotions, alcoholic and aqueous/alcohol solutions, emulsions, wax/fat compounds, stick preparations, powders or emollients, may contain mild surfactants, oil components, emulsifiers, superfatting agents, pearlizing waxes, consistency factors, thickeners, polymers, silicone compounds, fats, waxes, stabilizers, biogenic agents, deodorizers, antidandruff agents, film formers, swelling agents, UV protection  
15 factors, antioxidants, hydrotropes, preservatives, insect repellents, self-tanning agents, solubilizers, perfume oils, dyes, germ inhibitors and the like as further auxiliaries and additives.

The quantity in which the compounds according to the invention are used in cosmetic preparations is normally in the range from 0.01 to 5% by  
20 weight and preferably in the range from 0.1 to 1% by weight, based on the preparations.

For the production of pharmaceutical or even cosmetic preparations, the compounds of general formula (I) according to the invention, optionally in combination with other active principles may be incorporated together with one  
25 or more typical inert carriers and/or diluents, for example corn starch, lactose, cane sugar, microcrystalline cellulose, magnesium stearate, polyvinyl

pyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethylene glycol, propylene glycol, carboxymethyl cellulose or fat-containing substances, such as hard fat or suitable mixtures thereof, in typical galenic preparations, such as tablets, dragées, capsules, powders, suspensions, drops, ampoules, sirups or suppositories.

The daily dose required to obtain a corresponding effect in pharmaceutical applications is preferably 0.1 to 10 mg/kg body weight and more preferably 0.5 to 2 mg/kg body weight.

10

### Examples

#### Example 1: 6-O-phenylpropionyl-[2-(hydroxymethyl)phenyl]- $\beta$ -D-glucopyranoside

5 mmol D-(-)-salicin [2-(hydroxymethyl)phenyl- $\beta$ -D-glucopyranoside], 7.5 mmol phenylpropionic acid, 4 g molecular sieve, 4 ml t-butanol and 2.5 g immobilized lipase B from *Candida antarctica* were incubated for 34 hours at 60°C in a rotating 50 ml round-bottom flask. The reaction was monitored by thin-layer chromatography (silica gel 60 plates with fluorescence indicator; mobile solvent: chloroform/methanol/water 65/15/2 v/v/v; visualization: UV detection and with acetic acid/sulfuric acid/anisaldehyde (100:2:1 v/v/v) immersion reagent). The product was extracted with 20 ml of dichloromethane and purified by column chromatography (silica gel F60; mobile solvent: ethyl acetate/methanol 10/1 v/v). After purification, the yield was 32% (white solid).  $^{13}\text{C}$ -NMR ( $\text{CD}_3\text{OD}$ ):  $\delta(\text{ppm}) = 30.9$  (C-2), 38.7 (C-3), 61.6 (C-7\*), 65.2 (C-6'), 72.2 (C-4'), 75.6 (C-2'), 76.1 (C-5'), 78.4 (C-3'), 103.7 (C-1'), 117.6 (C-6\*), 124.5 (C-4\*), 127.6 (C-7), 130.1 – 131.0 (C-3\*, C-5\*, C-5, C-6, C-8, C-9), 132.8 (C-2\*), 143.4 (C-4), 157.5 (C-1\*), 175.2 (C'=O).

Example 2: 6-O-p-OH-phenylacetyl-([2-hydroxymethyl]phenyl)- $\beta$ -D-glucopyranoside

5 mmol D-(-)-salicin [2-hydroxymethyl]phenyl- $\delta$ -D-glucopyranoside], 7.5  
5 mmol *p*-OH-phenylacetic acid, 4 g molecular sieve, 4 ml *t*-butanol and 2.5 g  
immobilized lipase B from *Candida antarctica* were incubated for 34 hours at  
60°C in a rotating 50 ml round-bottom flask. The reaction was monitored by  
thin-layer chromatography (silica gel 60 plates with fluorescence indicator;  
mobile solvent: chloroform/methanol/water 65/15/2 v/v/v; visualization: UV  
10 detection and with acetic acid/sulfuric acid/anisaldehyde (100:2:1 v/v/v)  
immersion reagent). The product was extracted with 20 ml of dichloromethane  
and purified by column chromatography (silica gel F60; mobile solvent: ethyl  
acetate/methanol 10/1 v/v). After purification, the yield was 17% (white solid).  
 $^{13}\text{C}$ -NMR ( $\text{CD}_3\text{OD}$ ):  $\delta$  (ppm) = 41.8 (C-2), 61.0 (C-7\*), 65.0 (C-6'), 71.5 (C-4'),  
15 74.9 (C-2'), 75.4 (C-5'), 77.8 (C-3'), 103.2 (C-1'), 117.1 (C-6\*), 123.9 (C-4\*),  
129.4 - 132.3 (C-2\*, C-3\*, C-5\*; C-4, C-5, C-7, C-8), 136.1 (C-3), 156.0 - 159.2  
(C-1\*, C-6), 173.31 (C=O).

The following compounds were obtained in the same way as described  
20 in Example 1:

Example 3: *p*-chlorophenylacetyl-([2-(hydroxymethyl)phenyl]- $\beta$ -D-glucopyranoside

$^{13}\text{C}$ -NMR ( $\text{CD}_3\text{OD}$ ):  $\delta$  (ppm) = 41.2 (C-2), 61.0 (C-7\*), 65.1 (C-6'), 71.4 (C-4'),  
25 74.9 (C-2'), 75.2 (C-5'), 77.8 (C-3'), 103.1 (C-1'), 117.7 (C-6\*), 123.9 (C-4\*),  
129.5 - 132.0 (C-3 - C-5, C-7, C-8, C-2\*, C-3\*, C-5\*), 134.2 (C-6), 156.2 (C-1\*),

173.0 (C'=O).

Example 4: 6-O-cinnamoyl-([2-(hydroxymethyl)phenyl]- $\beta$ -D-glucopyranoside

$^{13}\text{C}$ -NMR ( $\text{CD}_3\text{OD}$ ):  $\delta$  (ppm) = 61.0 (C-7\*), 64.9 (C-6'), 71.8 (C-4'), 74.9 (C-2'),  
5 75.4 (C-5'), 77.9 (C-3'), 103.7 (C-1'), 117.1 (C-6\*), 118.6 (C-2), 123.8 (C-4\*),  
129.1 – 131.6 (C-5 bis C- 9, C-2\*,C-3\*, C-5\*), 135.6 (C-4), 146.5 (C-3), 156.2  
(C-1\*), 168.3 (C'=O).

Example 5: 6-O-oleoyl-([2-(hydroxymethyl)phenyl]- $\beta$ -D-glucopyranoside

10  $^{13}\text{C}$ -NMR ( $\text{CD}_3\text{OD}$ ):  $\delta$  (ppm) = 14.4 (C-18), 23.6 (C-17), 23.7 – 35.1 (C-11 bis  
C-16, C2 bis C-8), 60.9 (C-7\*), 64.7 (C-6'), 71.7 (C-4'), 74.9 (C-2'), 75.3 (C-5'),  
77.8 (C-3'), 103.6 (C-1'), 117.1 (C-6\*), 123.1 (C-4\*), 129.0 - 132.8 (C-9, C-10,  
C-2\*,C-3\*, C-5\*), 156.2 (C-1\*), 175.5 (C'=O).

15 Example 6: 6-O-palmitoyl-([2-(hydroxymethyl)phenyl]- $\beta$ -D-glucopyranoside

In a two-necked flask surmounted by a Soxhlet extractor (filled with  
activated molecular sieve), 0.5 g of immobilized *Candida antarctica* B lipase  
(SP 435, manufacturer Novo Nordisk) was added to 5 mmol D-(-)-salicin ([2-  
(hydroxymethyl)phenyl]- $\beta$ -D-glucopyranoside) and 5 mmol palmitic acid methyl  
20 ester in 50 ml acetone, followed by heating with stirring (magnetic stirrer, 200  
r.p.m.) under reduced pressure for 48 h to 40°C. The progress of the reaction  
was followed by thin-layer chromatography. After the end of the reaction, 14 g  
warm acetone (ca. 50°C) were added and the mixture was filtered at 50°C.  
The filtrate was cooled to -10°C and the product precipitated was isolated in a  
25 yield of 53% by filtration.

<sup>13</sup>C-NMR (CD<sub>3</sub>OD): δ (ppm) = 14.47 (C-16), 23.74 (C-15), 26.00 (C-3), 30.22 - 30.80 (C-4 - C-13), 33.08 (C-14), 35.03 (C-2), 60.98 (C-7\*), 64.59 (C-6'), 71.64 (C-4'), 74.96 (C-2'), 75.49 (C-5'), 77.82 (C-3'), 103.22 (C-1'), 117.07 (C-6\*), 123.82 (C-4\*), 129.78 - 132.34 (C-2\*, C-3\*, C-5\*), 156.98 (C-1\*), 175.23 (C=O). Anal. calculated for C<sub>29</sub>H<sub>48</sub>O<sub>8</sub> (524.69): C, 66.39; H, 9.22. Found: C, 67.88; H, 9.41.

Examples 7 to 9: preparation of other salicin esters by transesterification:

Salicin ([2-(hydroxymethyl)phenyl]-β-D-glucopyranoside) was reacted with various carboxylic acid methyl esters by the method described in Example 6 and the salicins selectively esterified at the primary alcohol function of the glucose unit listed in the following Table were obtained.

Compound	Reaction temperature	Reaction time	Yield
Salicin stearate (Example 7)	40°C	24 h	67%
Salicin myristate (Example 8)	35°C	48 h	29%
Salicin phenyl acetate (Example 9)	35°C	48 h	32%

The salicin esters thus prepared were characterized by NMR spectroscopy; the spectrum of Example 9 is shown by way of example below:

6-O-phenylacetyl-([2-(hydroxymethyl)phenyl]-β-D-glucopyranoside) (Example 9)

<sup>13</sup>C-NMR (CD<sub>3</sub>OD): δ (ppm) = 41.82 (C-2), 60.99 (C-7\*), 65.03 (C-6'), 71.52 (C-4'), 74.94 (C-2'), 75.49 (C-5'), 77.77 (C-3'), 103.21 (C-1'), 117.11 (C-6\*),

123.91 (C-4\*), 127.89 (C-6), 129.46 - 132.37 (C-2\*,C-3\*, C-5\*; C-4, C-5, C-7, C-8), 136.12 (C-3), 156.95 (C-1\*), 173.31 (C=O). Anal. calculated for  $C_{21}H_{24}O_8$  (404.41): C, 62.38; H, 5.98. Found: C, 63.96; H, 5.90.

5 Example 10: cytotoxicity (in mouse or human skin keratinocytes, MSCP 5 or HPK II)

The toxicity of the substances was investigated by the MTT Test (Mosmann 1983) in cell cultures. This test is based on the conversion of the yellow tetrazolium salt MTT into the violet dye formazane. The reaction takes  
10 place only in living cells through the succinate dehydrogenase located in the inner mitochondrial membranes. On account of the potential use in cosmetic or pharmaceutical products, skin cells (human HPKII or mouse MSCP 5 keratinocytes) were used as the test system. The substances tested (phenylpropionyl salicin and p-OH-phenyl acetyl salicin) were non-toxic to the  
15 cells in concentrations in which they showed biological activity (inhibition of prostaglandin synthesis). The effect of the substances on the keratinocytes was independent of the time (incubation time 1.5 or 20 h), the growth state (confluent or subconfluent) and the organism (mouse or human).

Figure 1 shows that the influence of phenylpropionyl salicin (lower solid-line curve) and p-OH-phenylacetyl salicin (upper dotted-line curve) on the  
20 vitality of skin cells (keratinocytes) was minimal. The substances were dissolved in the culture medium and incubated with the cells for 20 h. The MTT reduction test was then carried out with fresh medium without test components.

25

Example 11: inhibition of prostaglandin synthesis by salicin derivatives (in

mouse or human skin keratinocytes MSCP 5 or HPK II)

Figure 2 shows the inhibiting effects of salicin and salicin esters on the release of prostaglandins in keratinocytes. The cells were marked for 16 hours with  $0.2 \mu\text{Ci } ^{14}\text{C}$ -arachidonic acid  $\text{ml}^{-1}$  medium. The test substances were added in fresh medium with increasing concentrations and incubated for 2 hours. In the Figure, the substances have the following meanings:

1 = negative control

2 = salicin

3 = phenylpropionyl salicin

10 4 = p-OH-phenyl acetyl salicin

5 = positive control

In the positive control NS398 ( $10 \mu\text{M}$ ) for MSCP5 cells, prostaglandin synthesis is reduced by 85%. The prostaglandins were identified by comparison with reference substances and quantified by radiosensitometry.

15 The result is expressed as the average value of three measurement points:  
MSCP 5: 100% = 201 cpm; HPK II: 100% = 63 cpm.

Example 12: influencing of the transcription activity of HPK II (human skin keratinocytes)

20 The release of prostaglandins can be influenced by inhibitors at several levels. Besides inhibition of the catalytic activity of the prostaglandin synthase proteins, another possible effect is on the messenger RNA of the cyclooxygenases. It was found in *Northern Blot* analyses that, when subconfluent MSCP 5 cells are incubated for 45 mins. with  $500 \mu\text{M}$  p-OH-phenylacetoyl salicin, the COX-2-mRNA *steady state* concentration is greatly  
25 reduced by comparison with untreated cells. As a negative control, the cells

were incubated for 45 minutes in medium containing only the solubilizer acetone (0.25% v/v) but no test substance for the same recorded RNA concentration.

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**CLAIMS**

1. Salicyl alcohol derivatives corresponding to general formula (I):



5

in which  $R^1$  is a hydrogen atom or a  $C(O)R^3$  group where  $R^3$  is an alkyl, cycloalkyl, cycloalkylalkyl, aralkyl or aryl group containing 1 to 26 carbon atoms and/or 1-10 hetero atoms which may be unbranched or branched, mono- or polyunsaturated and/or may bear substituents on the carbon chain and/or at the hetero atoms,

10

Ph is the 1,2-phenylene group,

Z is a sugar hemiacetally attached to the aromatic group Ph in (I) and optionally substituted n-times by  $R^2$  like an ester; the sugar may be a mono-, di-, oligo- or polysaccharide,

15

n is an integer between 0 and m, m being equal to the number of free hydroxyl groups present in the sugar Z hemiacetally attached to the aromatic group,

$R^2$  is a hydrogen atom or a group  $C(O)R^4$  where  $R^4$  is selected from the same group as  $R^3$ ;  $R^1$  and  $R^2$  may be the same or different with the proviso that at most one of the two substituents  $R^1$  or  $R^2$  is hydrogen when Z is glucose,

20

and on the conditions that

where Z is glucose and  $R^2$  is hydrogen,  $R^1$  cannot be acetyl or benzoyl or (1-hydroxy-6-oxo-2-cyclohexen-1-yl)carbonyl and, where  $R^1$  is hydrogen, Z is glucose and  $n = 1$  and the glucose unit is substituted by  $R^2$  at its primary hydroxy group,  $R^2$  cannot be 4-phenylbutyryl.

25

2. Salicyl alcohol derivatives as claimed in claim 1, characterized in that at least one of the two substituents  $R^1$  and  $R^2$  is a hydrogen atom, the benzoyl,

phenylacetyl, phenylpropionyl, phenylbutyryl, phenylvaleroyl, o-, m- or p-hydroxybenzoyl, o-, m- or p-hydroxyphenylacetyl, o-, m- or p-hydroxyphenylpropionyl, o-, m- or p-hydroxyphenylbutyryl, o-, m- or p-hydroxyphenylvaleroyl, 3,4,5-trihydroxybenzoyl, 3-phenylacryloyl, o-, m- or p-hydroxy-3-phenylacryloyl or 3-(3,4-dihydroxyphenyl)-acryloyl group.

3. Salicyl alcohol derivatives as claimed in at least one of claims 1 and/or 2, characterized in that  $n = 1$  and  $R^1$  is hydrogen.

4. Salicyl alcohol derivatives as claimed in at least one of claims 1 to 3, characterized in that Z is a monosaccharide selected, for example, from  
10 threose, erythrose, arabinose, lyxose, ribose, xylose, allose, altrose, galactose, glucose, gulose, idose, mannose, talose and fructose, the naturally occurring stereoisomers of the sugars being preferred.

5. Salicyl alcohol derivatives as claimed in at least one of claims 1 to 4, characterized in that Z stands for D-glucose.

15 6. Salicyl alcohol derivatives as claimed in claim 1, characterized in that, where  $R^1$  is hydrogen, Z is glucose and  $n = 1$  and the glucose is substituted by  $R^2 = C(O)R^4$  at its primary hydroxy group,  $R^4COOH$  is not a hydrophobic aromatic carboxylic acid.

7. A process for the production of the compounds claimed in at least one  
20 of claims 1 to 6, characterized in that an alcohol component is esterified or transesterified with a carboxylic acid, a carboxylic acid ester or an activated carboxylic acid derivative in the presence of suitable catalysts.

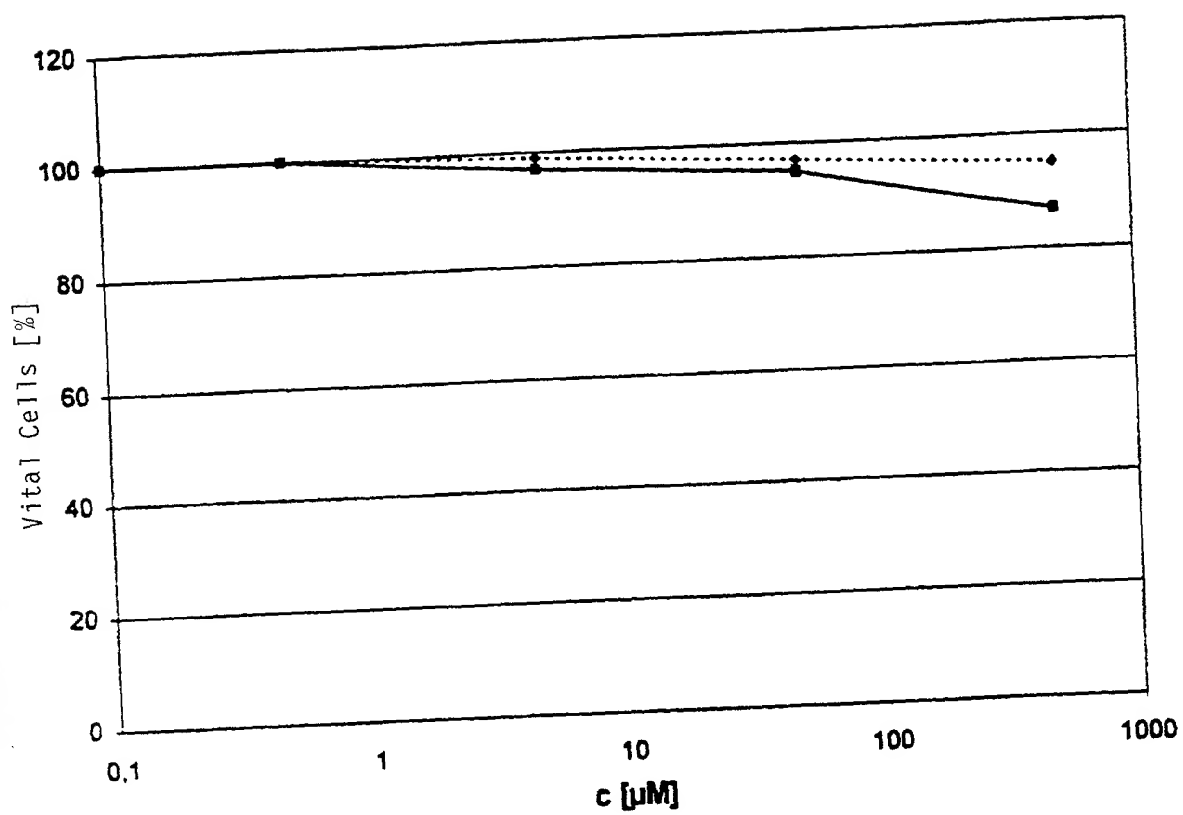
8. A process as claimed in claim 7, characterized in that production is carried out by enzyme-catalyzed esterification or transesterification.

25 9. The use of the compounds claimed in at least one of claims 1 to 6 for the production of cosmetic and/or pharmaceutical preparations.

10. Cosmetic preparations, characterized in that they contain the salicyl alcohol derivatives claimed in at least one of claims 1 to 6.

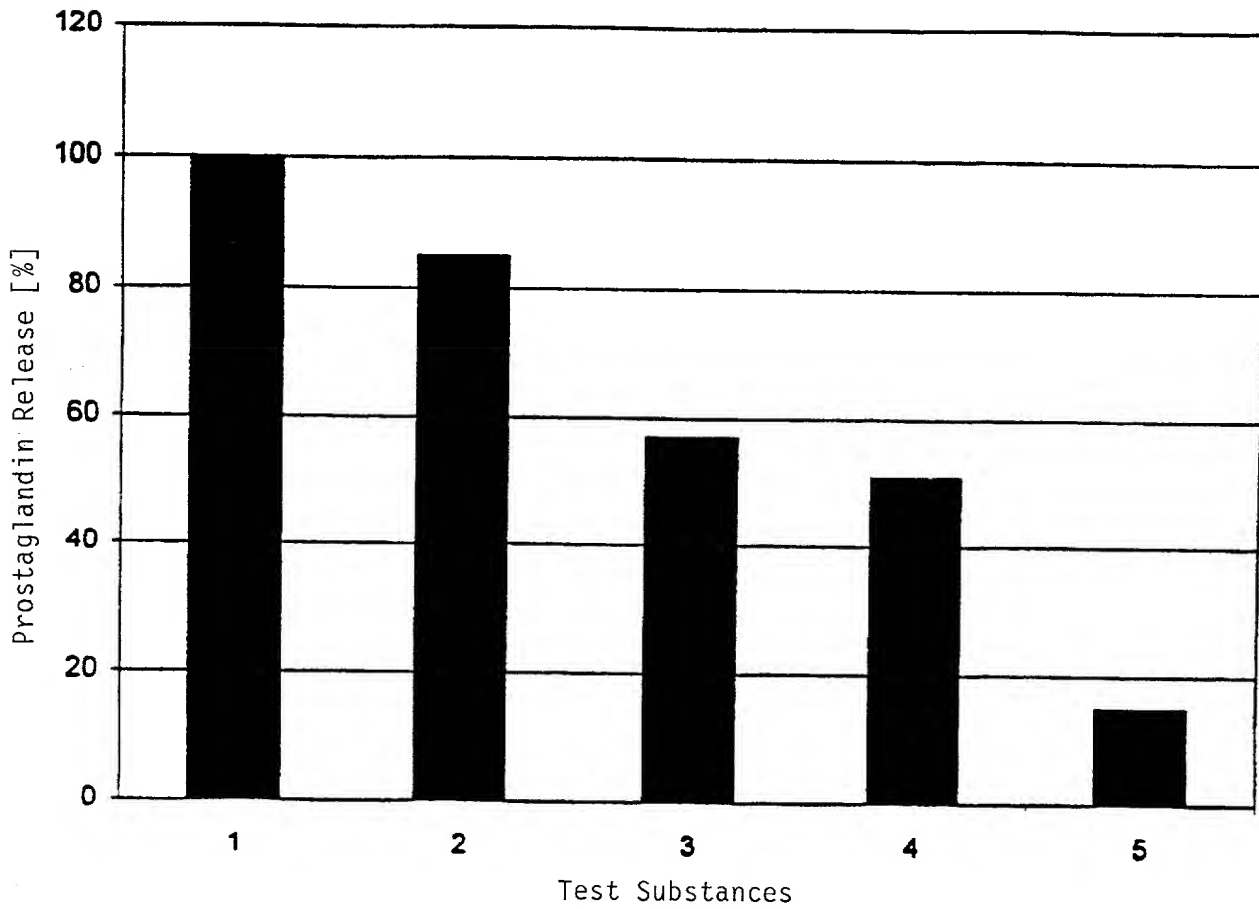
11. Pharmaceutical preparations, characterized in that they contain the salicyl alcohol derivatives claimed in at least one of claims 1 to 6.

Fig. 1

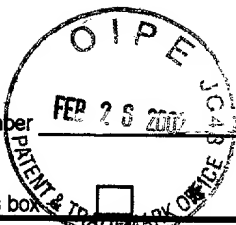


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Fig. 2



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## DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION

☐ Declaration Submitted with Initial Filing OR ☐ Declaration Submitted after Initial Filing

Attorney Docket Number

H 4148 PCT/US

First Named Inventor

OTTO, Ralf

COMPLETE IF KNOWN

Application Number

Filing Date

Group Art Unit

Examiner Name

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

NOVEL SALICYL ALCOHOL DERIVATIVES

(Title of the Invention)

the specification of which

☐ is attached hereto

OR

☒ was filed on (MM/DD/YYYY)

04/28/2000

as United States Application Number or PCT International

Application Number

PCT/EP00/03758

and was amended on (MM/DD/YYYY)

(if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37 Code of Federal Regulations, § 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code §119(a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT International application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached?	
				YES	NO
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☐ Additional foreign application numbers are listed on a supplemental priority sheet attached hereto:

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Application Number(s)	Filing Date (MM/DD/YYYY)	<input type="checkbox"/> Additional provisional application numbers are listed on a supplemental priority sheet attached hereto.

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## DECLARATION

Page 2

I hereby claim the benefit under Title 35, United States Code §120 of any United States application(s), or §365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of Title 35, United States Code §112.1 acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application Number	PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number (if applicable)
	PCT/EP00/03758	04/26/2000	

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Name	Registration Number	Name	Registration Number
Wayne C. Jaeschke	21,062	Glenn E. J. Murphy	33,539
Kimberly R. Hild	39,224	Stephen D. Harper	33,243

☐ Additional attorney(s) and/or agent(s) named on a supplemental sheet attached hereto.

Please direct all correspondence to: ☒ Customer Number or label CUST NO. 00423 OR ☐ Fill in correspondence address below

Name	Glenn E. J. Murphy				
Address	Henkel Corporation - Patent Department				
Address	2500 Renaissance Boulevard, Suite 200				
City	Gulph Mills	State	PA	ZIP	19406
Country	USA	Telephone	610-278-4926	Fax	610-278-6548

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor: ☐ A petition has been filed for this unsigned

Given Name	Ralf	Middle Initial		Family Name	OTTO	Suffix e.g. Jr.	
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Inventor's Signature		Date	07.06.01
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Residence: City	Bad Friedrichshall	State		Country	Germany	Citizenship	Germany
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Post Office Address	Oedheimerstr. 6
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City	74177 Bad Friedrichshall	State		Zip		Country	Germany	Applicant Authority	
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☒ Additional inventors are being named on supplemental sheet(s) attached hereto

**DECLARATION****ADDITIONAL INVENTOR(S)  
Supplemental Sheet**

Name of Additional Joint Inventor, if any:

☐ A petition has been filed for this unsigned inventorGiven  
Name

Albrecht

Middle  
InitialFamily  
Name

WEISS

Suffix  
e.g. Jr.Inventor's  
Signature*Albrecht**Weiss*

Date

21.06.01

Residence:  
City

Langenfeld

State

Country

Germany

Citizenship

Germany

Post Office Address

Forellenweg 37

Post Office Address

City

40764 Langenfeld

State

Zip

Country

Germany

Applicant  
Authority

Name of Additional Joint Inventor, if any:

☐ A petition has been filed for this unsigned inventorGiven  
NameMiddle  
InitialFamily  
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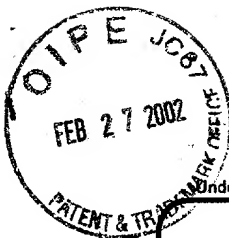
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37 FEB 2002 PTO/SB/123 (40-00)

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First Named Inventor

OTTO, Ralf

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Attorney or agent of record.

Typed or  
Printed Name

Glenn E. J. Murphy, R.N. 33,539

Signature

Date

2/14/02

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PATENT  
Docket No. H 4148 PCT/US (now C 2378)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re: Application of Otto, et al.

Serial No. 09/856,835      Examiner:  
Filed: Unknown      Art Unit:  
TITLE: NOVEL SALICYL ALCOHOL DERIVATIVES

**APPOINTMENT OF ASSOCIATE ATTORNEY AND/OR AGENT**

Commissioner for Patents  
Washington, D.C. 20231

Sir:

I, Glenn E. J. Murphy, hereby appoint **John E. Drach (Reg. No. 32,891)**, **Aaron R. Ettelman (Reg. No. 42,516)**, **Steven J. Trzaska (Reg. No. 36,296)** and **Henry E. Millson, Jr. (Reg. No. 18,980)** as Associate Attorney and/or Agent as provided in 37 CFR 1.34 to transact all business with the U.S. Patent and Trademarks Office in connection with the above application and any continuation, division, and/or continuation-in-part thereof, and hereby ratify any and all acts done prior to such appointment in connection with the above application.

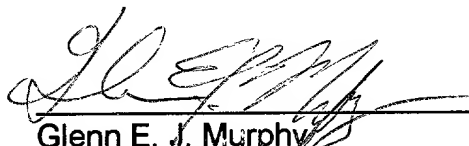
Address all correspondence to:

John E. Drach  
Cognis Corporation, Patent Dept.  
2500 Renaissance Blvd., Suite 200  
Gulph Millis, PA 19406

Direct all telephone calls to:

John E. Drach  
610-278-4925

Respectfully submitted,

  
\_\_\_\_\_  
Glenn E. J. Murphy  
(Reg. No. 33,539)  
Attorney of Record

Date: 07/14/02